

REMARKS

This Amendment is in reply to the Office Action dated December 29, 2004. Applicants respectfully submit that this Amendment constitutes a submission pursuant to 37 CFR 1.114. Reconsideration and allowance of the above-identified patent application are respectfully requested. This application relates to a method of treating migraine and pharmaceutical compositions.

Claims 1 to 20 are currently pending in the application. Claims 3, 4, 7 to 10 and 17 have been withdrawn from consideration as drawn to non-elected species. Claim 15 is also directed to a non-elected species but was not withdrawn by the Examiner. Applicants believe this was an oversight and have treated Claim 15 as withdrawn from consideration for purposes of this Amendment. Upon the allowance of a generic claim, Applicants respectfully request consideration of the additional species that are written in dependent form or otherwise include all the limitations of the allowed generic claim as provided by 37 CFR 1.141.

Claims 1, 2, 5, 6, 11 to 14, 16 and 18 stand rejected under 35 U.S.C. 103(a) over WO 02/089798 A2 (Allen) and Gallagher et al., Headache, 1987, vol. 27, no. 2, pages 84-86 (Gallagher). Claims 1, 2, 5, 6, 11 to 14, 16 and 18 stand rejected under 35 U.S.C. 103(a) over U.S. No. 6,384,034 (Simitchieva) and Gallagher. No claim has been allowed.

This Amendment cancels Claims 19 and 20. Upon entry of this Amendment, claims in the application are Claims 1 to 18.

Applicants respectfully traverse the obviousness rejection of Claims 1, 2, 5, 6, 11 to 14, 16 and 18 over Allen and Gallagher. Allen is directed to a method for treating or preventing migraine by administering to the patient an effective amount of etoricoxib. As stated by the Examiner, Allen teaches that etoricoxib may be administered in combination with other agents but fails to mention timolol.

Gallagher teaches that 10-30 mg of timolol once daily reduced the frequency of common migraine attacks in a 116 patient study.

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. See M.P.E.P. § 2142. In the instant case, one of ordinary skill in the art with knowledge of Allen and Gallagher would in no way have been motivated to combine these two references to arrive at the present invention. There are numerous analgesic and anti-migraine medications known to the ordinarily skilled artisan to treat or prevent migraine. The Examiner has failed to sufficiently explain why the ordinarily skilled artisan would select the claimed combination of a cyclooxygenase-2 inhibitor and beta blocker out of the vast number of other possible combination therapies. The Examiner cites *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980) for the proposition that the “motivation for combining the components flows from their individually known common utility.” However, the Examiner’s reliance on *In re Kerkhoven* is misplaced. That opinion related to methods of producing mixed active particulate detergents and not combining medications for treating or preventing migraine. Furthermore, Applicants respectfully refer the Examiner to *In re Geiger*, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987), which states that “obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.”

In the present case, Applicants submit that common utility alone does not provide the necessary motivation. “The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination.” See M.P.E.P. § 2143.01. Obvious to try is not the proper standard under which to make a determination of obviousness. There must be the necessary motivation for those of ordinary skill to make the combination and a clear direction that the combination of references would have led one of ordinary skill in the art to the present invention. In the instant case, the necessary motivation and a clear direction are not conveyed by the references alone or in combination.

Furthermore, the Examiner acknowledges that Allen lists numerous medications that can be combined with etoricoxib, but fails to mention timolol. This omission further evidences that the claimed combination is not obvious by teaching away from the claimed

combination. Otherwise, if the combination is obvious, it surely would have been listed in Allen with the others.

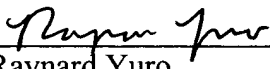
Applicants also respectfully traverse the obviousness rejection of Claims 1, 2, 5, 6, 11 to 14, 16 and 18 over Simitchieva and Gallagher. Simitchieva is directed to a combination of a cyclooxygenase-2 inhibitor and a 5-HT_{1B/1D} agonist for treating or preventing migraine. The Examiner states that it “would have been obvious to one of ordinary skill in the art to employ combinations of etoricoxib and timolol maleate for the treatment of migraine because all components are well known individually for treating migraine.” However, Simitchieva teaches the combination of a COX-2 inhibitor and a 5-HT_{1B/1D} agonist, not the COX-2 inhibitor alone. Thus, one having ordinary skill in the art would have to replace the 5-HT_{1B/1D} agonist with timolol maleate to arrive at the present invention, even though there is no suggestion in Simitchieva to do so.

Applicants submit that one having ordinary skill in the art with knowledge of Simitchieva would in no way be motivated to substitute timolol maleate for a 5-HT_{1B/1D} agonist based on the teachings of Gallagher. The Examiner has failed to sufficiently explain why the ordinarily skilled artisan would be motivated to select timolol out of the multitude of other anti-migraine medications available and substitute timolol for the 5-HT_{1B/1D} agonist taught in Simitchieva. Applicants respectfully submit that the Examiner is applying an improper “obvious to try” rationale in support of the obviousness rejection. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. See *In re Geiger* at 1278.

Serial No.: 10/767,025
Case No.: 21311
Page 8

Applicants respectfully submit that the application is in condition for allowance and passage thereto is earnestly requested. Any additional fees required in connection with this Amendment may be taken from Merck Deposit Account No. 13-2755. The Examiner is invited to contact the undersigned attorney at the telephone number provided below if such would advance the prosecution of the case.

Respectfully submitted,

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